REMARKS

This paper is being filed in response to the Office Action dated June 17, 2002 that was issued in the above-identified application.. Applicants request a three-month extension of time and enclose the fee required under 37 C.F.R. §1.17(a)(3). Applicants also enclose a Substitute Sequence Listing in paper and computer-readable form and a Supplemental Combined Declaration and Power of Attorney (unexecuted). Applicants respectfully request reconsideration of the above-identified application in light of the amendments and remarks presented in the instant Amendment.

Claims 1-14 are pending. Claims 2-6 have been cancelled without prejudice. New claims 38-40 have been added. Claims 1, 7, and 11 have been amended. Claims 1, 7-14, and 38-40 will be pending after entry of the instant Amendment.

Rewritten claims and specification paragraphs appear in the preceding "IN THE CLAIMS" and "IN THE SPECIFICATION" sections, respectively. Attached hereto is a marked-up version of the changes made by the instant amendment captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and is included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE CLAIMS" and "IN THE SPECIFICATION" sections shall take precedence.

Amended claims 1, 7 and 11, new claims 38-40, the amended specification paragraphs, the Substitute Sequence Listing are fully described and supported by the application as filed. To more clearly illustrate the support for the sequence ranges recited in the amended claims, new claims, specification paragraphs, and Substitute Sequence Listing, Applicants have prepared the Figure on the following page.

	SEQ ID NO:1	Fig. 2
ACATGGGCAC GCGTGGTCGA CGGCCCGGGC TGGCTGGGCA ACACGGGTTC AGCCCAGGTT TCATAGTAAG TTCCAGACAC	80	-1697
TCCTGGAAAA ACAATACAGG TCCCTGACAA AAGAAAAAAC AAAACAAAGG AAACAGAAAC ATGCGTTTTT AAAAAAGAAG	160	-1617
GAGGAGACTC CATGAAGGCA GGCCTTGGGT GGGGTCACTG CTTCTCTGTA CACAGGAGGA GAATTGCCAA GATCTTCCGG	240	-1537
ACAGTGTGGA CTATACTGTA AGACCCTCTC AATACAGACA GACTGGACAG GCATAGTGAC ACATGCCTTT AATGCCTGCA	320	-1457
GTACTCAGGA GGAGGTGGCA GGTGGAACGG CTGTTCTTTG AGGTTCAAGA CCAGCGTGGA CTACAGAGTG AGTTCCAGGA	400	-1377
CAGGCAGGGC TACACAGAAA AATCCTGTCT GAAAACAAAA CAAAACCCAG ACAGACACAC CAAAAACAGC CAAGGGACCA	480	-1297
GAGAGATGGG TCAGGGCCTA ATCACTTGCT ACTCTTTGCA GAGGACCCAA ATTTAGTTCC TATAACCCTC CATGAGAAGC	560	-1217
TTCACAATTG TCTCTAACTC AATTCCACCC GTGTTCCGAC CTCCCATATG CACCAGACAT GTTATACTCA CACATACGCA	640	-1137
CAAACACACA CACACACACA CACACACACA CACACACACA CACACACACA CGGAAAACAT ATAAAATAAA GATTTAAAAA	720	-1057
ATCTTTTTCT TTTGGCCGGG GTGTGTGGGA GAGCATCTGA GCCATCTCAC CAGCCCAGGG TGCACGTCTT TTTCTTTTTT	800	-977
TCGGAGCTGG GGACCGAACC CAGAGCCTTG TGCTTGCTAG GCAAGTGCTC TACCACTGAG CTAAATCCCC AACCCCGGAG	880	-897
CACGTCTTTA ATCCCAGAAT CAGGAGGTAG AGGTAATGAG ATCCCAGTGA GCCCAAGGTC AGCCGAGTCT ACAAAGTGAG	960	-817
TTCCAGGACA GCCAGAACTA ATCTTGGAAA AACAAACAAG GGCTGGTGAG GTGGTTCAGT AGTTAAGAAC ACTGGCTGCT	1040	-737
CTTCCAGAGG TCCTGAGTTC ATTCTCAGTA ACCACATGGT GGGGATCTGA TGCCTGTTCT GGCATGCAGA TATACATGCA	1120	-657
GATAGTGCAC TCCTACATTT AAAAAAAAAA GACATAAATA ATATTTTAAA ACATTGGGCG TTTTGTCTTC TAATAAAACT	1200	-577
TCACTGCTAT CTTCTAATAA AAATTCACTG CTAGCCGCGG GGTGTGGTGC CCCCATACCT TTAATCCCAA CAACTTGAGA	1280	-497
GGCAGAGGCA GGCGGACCTT TGAGTTTGAA GCTAGCCTGG TCTACAGAGT GAGTTCAAGA TAGCCACGGA TAGTCAGAAA	1360	-417
GTCCTGTTTC GAACCTCTCC CCAACCAAAT CACTCCTGTA ATCCCAGCAC TCTGGAGGCA GTAGCAGGTT AGTCCCTGCT	1440	-337
TCTCAGAGAG AGGAGAGAGA GAGAGAGAGA GAGGAGACAC ACACACACAG AGACAGAGAG GAGAGA	1520	-257
	1600	-177
PEA3	1680	-97
TATA box	1760	-17
AP1 A	1840	+64
	1920	+144
	1970	+194

Nucleotides shown in red correspond to the beginning and ending nucleotides of PEG3-Prom, which is highlighted in blue. The nucleotide in the +1 position of Figure 2 is shown in white with a darker shade of blue highlight. This Figure demonstrates that the sequence ranges recited in the amended claims correspond to the ranges shown in Figure 2 as originally filed as follows:

	Original Specification	Original Figure 2	Original SEQ ID NO:1
Full-length Sequence	--	-1777 to +194	1 to 1970
PEG3-Prom	-270 to +194 (page 7, lines 14-17)	-270 to +194	1507 to 1970
PEA3 site	-105 to -100 (page 7, line 25-28)	-105 to –100	1672 to 1677
TATA box	-29 to -24 (page 7, lines 30-32)	-29 to –24	1746 to 1753
AP1 site	+6 to +12 (page 8, lines 1-4)	+5 to +11	1781 to 1787

Amended claim 1 is supported by, *inter alia*, original claim 1 and Figure 2. Amended claims 7 and 11 are supported by, *inter alia*, original claims 7 and 11 . New claim 38 is supported by the specification at, *inter alia*, page 10, lines 21-31, Figure 2 and original claims 1, 3, and 5. New claims 39 and 40 are supported by the specification at, *inter alia*, page 10, lines 21-31, page 14, lines 20-23, Figure 2 and original claims 1, 3, and 5.

Applicants have claimed priority to U.S. Patent Application No. 09/052,753, filed March 31, 1998. This claim of priority is proper since (1) the applications share a common inventor, Dr. Paul B. Fisher, (2) the applications are copending, (3) the instant application has been amended to contain a specific reference to the earlier application, and (4) both applications relate to the PEG-3 promoter. Since this application was filed before November 29, 2000, the amendment to 35 U.S.C. § 120 authorizing the Director to limit the period of time for submission of priority claims made by Section 4503 of the American Inventor's Protection Act of 1999 does not apply to this application. This assertion, however, should not be construed as an admission that the priority claim is not warranted under current law. On the contrary, Applicants reserve all

rights related to this priority claim including, *inter alia*, the right to make a showing of unintentional or unavoidable delay. As part of the priority claim, a Supplemental Combined Declaration and Power of Attorney is enclosed, which is as yet unexecuted. An executed version will follow.

The Sequence Listing of record has been replaced with a Substitute Sequence Listing. Support for this amendment may be found in the specification as originally filed, *inter alia*, at page 7, line 25 to page 8, line 4 and Figure 2, and at page 56 lines23-30 and Figure 2.

The paragraph beginning at page 2, line 3 and ending at page 2, line 26 has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at Figure 2, SEQ ID NO:1, page 29, lines 17-27, and page 36, lines 15-28.

The paragraph beginning at page 7, line 19 and ending at page 7, line 21 has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at claim 1.

The paragraphs beginning at page 7, line 25 and ending at page 8, line 4 have been amended. Support for these amendments may be found in the specification as originally filed, *inter alia*, at Figure 2 and SEQ ID NO:1.

The paragraph beginning at page 10, line 13 and ending at page 10, line 19 has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at page 29, lines 17-27 and page 36, lines 15-28.

The paragraph beginning at page 10, line 21 and ending at page 10, line 31 has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at Figure 2 and SEQ ID NO:1.

The paragraph beginning at page 44, line 20 and ending at page 45, line 22 has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at Figure 5A.

The paragraph beginning at page 56, line 22 and ending at page 57, line 9, has been amended to conform with changes in the Sequence Listing, as discussed below.

The abstract has been amended. Support for this amendment may be found in the specification as originally filed, *inter alia*, at the abstract, page 29, lines 17-27, and page 36, lines 15-28.

Therefore, all amendments made by the instant Amendment are fully supported by the application as filed and, therefore, do not constitute new matter.

I. Substitute Sequence Listing Complies with Requirements

As a preliminary matter, Applicants thank the Examiner for correcting minor errors in the sequence listing. Nevertheless, Applicants submit herewith a Substitute Sequence Listing in paper and computer readable form. The amendments are as follows.

First, Applicants have amended the description of the features of SEQ ID NO:1 to correlate the numbering of SEQ ID NO:1 with the numbering shown in Figure 2.

Second, the directionality of SEQ ID NOS: 6, 8, 10 and 12 has been changed. The Examiner's attention is invited to the specification at page 56 lines 22-30. A variety of probes are described. Each probe is presented as a pair of apparently complementary nucleic acids; for example, considering the wild-type AP1 probe, the first 5 nucleotides of SEQ ID NO:5, CGCAG, are complementary to the first five nucleotides of SEQ ID NO:6, GCGTC; however, for this complementarity to apply, one of the sequences must be in the 5' – 3' direction, and the other in the 5'-3' direction. Comparing the sequences with those in Figure 2 indicate that

SEQ ID NOS: 5, 7, 9 and 11 are in the 5' – 3- direction, indicating that their complementary sequences, SEQ ID NO: 6, 8, 10 and 12, are in the 3' – 5' direction. The Sequence Listing has been amended accordingly; note that because the recited sequences must be provided 5'-3' (37 C.F.R> §1.822(c)(5)), the original sequences are reversed by this amendment. The specification is amended to conform with this amendment. Because this is a clear and obvious error, the aamendment does not constitute new matter.

I hereby state that the content of the paper and computer readable copies of the Substitute Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), are the same. I hereby state that the content of the paper and computer readable copies of the Substitute Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(g), herein does not include new matter.

II. Drawing Complies with Requirements

The Examiner has objected to Figure 2 for allegedly depicting the +1 site incorrectly with respect to the AP1 site as described at page 8, lines 3-4, page 10, lines 29-30, and claim 3.

Applicants traverse this objection and assert that Figure 2 does not require correction. Instead, Applicants have cancelled claim 3 and amended the description at page 8, lines 3-4, and at page 10, lines 29-30 to indicate that the location of the AP1 site is from +5 to +11, which is in agreement with Figure 2 and, hence, does not constitute new matter. Therefore, Applicant's respectfully request withdrawal of this objection.

III. Specification Complies with Requirements

The Examiner has objected to the abstract as allegedly exceeding 150 words in length. Applicants submit herewith a substitute abstract on a separate sheet. Applicant's assert that the substitute abstract complies with 37 C.F.R. §1.72(b) and MPEP §608.01(b) and, therefore, respectfully request withdrawal of this objection.

The Examiner has objected to the specification as identifying the deletion depicted in Figure 5A, Fragment 11 as deleted from nucleotide –1267 on page 45, line 17, while the figure appears to show that the deletion is from nucleotide –1167. The Examiner has further objected to the specification as identifying the deletion depicted in Figure 5A, Fragment 6 as deleted from nucleotide –1267 to –536 on page 45, line 9 while the figure appears to show that the deletion is from nucleotide –1267 to –361. The specification has been amended to conform with Figure 5A.

Since the paragraph on page 45, as amended herein, agrees with Figure 5A, Applicants respectfully request withdrawal of this objection.

IV. Claims Comply With 35 U.S.C. §112, First Paragraph

A. Claims Comply With Written Description Requirement

The Examiner has rejected claims 2-14 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to convey to an artisan of ordinary skill that the inventors had possession of the claimed invention at the time the application was filed. The Examiner has alleged that Applicants only disclose various deletion and truncation mutants that are much larger than 15 nucleotides and that no 15 nucleotide sequence could contain all three domains that the description identifies as necessary for promoter activity.

Applicants traverse this rejection and assert that the claims, as amended herein, recite subject matter that was sufficiently described to indicate to one of ordinary skill in the art that Applicants had possession of the invention at the time the application was filed. Claims 2-6 have been cancelled. Therefore, this rejection is moot with respect to these claims. Claims 7-14 have been amended to be dependent on independent claim 1. Therefore, Applicants respectfully request withdrawal of this rejection as to claims 7-14.

New claims 38-40 are supported by the specification as filed, *inter alia*, at page 10, lines 21-31, page 14, lines 20-23, Figure 2 and original claims 1, 3, and 5. Applicants assert that the artisan of ordinary skill would recognize that Applicants had possession of the claimed invention in view of Applicant's disclosure of the PEA3 site, the TATA box, and the AP1 site as the three elements required for differential expression of PEG-3. *See e.g.* page 48, line 33 et seq. Therefore, Applicants believe that claims 38-40 comply with the written description requirement.

B. Claims Comply With Enablement Requirement

1. Nucleic Acids Are Fully Enabled

The Examiner has rejected claims 2-5 and 7-14 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not enabled by the specification as filed. The Examiner has acknowledged that the specification is enabling for an isolated nucleic acid comprising a fragment of the nucleotide of claim 1 which is at least 15 nucleotides in length and which has PEG-3 promoter activity. However, the Examiner has alleged that the specification does not provide enablement for an isolated nucleic acid that does not have PEG-3 promoter activity. Specifically, the Examiner has alleged that one of ordinary skill in the art would be required to engage in undue experimentation to determine the function of each

fragment of SEQ ID NO:1 of 15 nucleotides or more that lacks promoter activity, if any, and then determine if there is a use for each such fragment.

Applicants traverse this rejection and assert that the claims, as amended herein, are fully enabled. This rejection is moot as to claims 2-5 since these claims have been cancelled. Claims 7-14 have been amended to be dependent on claim 1. Therefore, Applicants respectfully request withdrawal of this rejection.

New claims 38-39 recite the term "PEG-3 promoter activity". Applicants assert that this term necessarily indicates that the claimed nucleic acid has promoter activity, thereby obviating any need for the artisan of ordinary skill to engage in undue experimentation. Therefore, Applicants believe that independent claims 38 and 39 and dependent claim 40 are fully enabled by the specification as filed.

2. Gene Therapy And Other Uses Are Fully Enabled

The Examiner has further rejected claims 10-14 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not enabled by the specification as filed. The Examiner has alleged that the only use for a nucleic acid comprising nucleotides –270 to +194 of SEQ ID NO:1 linked to a tumor suppressor gene is gene therapy. The Examiner has further alleged that, as of Applicant's filing date, there was a complete lack of documented success for any gene therapy treatment and has cited documents published between 1997 and 2000 to support this allegation.

Applicants traverse this rejection and assert that these claims are fully enabled by the specification as filed with respect to gene therapy and other uses. Applicant's assert that the documents cited by the Examiner do not accurately reflect the state of this fast-moving field of art as of Applicant's filing date. For example, the Examiner has cited Verma and Somia, 1997,

Nature 389:239 to support an allegations related to the obstacles remaining in the gene therapy art. However, as of November 2000, Verma and Somia recanted their pessimism and expressed a more optimistic view. *See* Somia and Verma, 2000, *Nat Rev Genet.* 1(2):91-99 (hereinafter "Somia"). After describing the work Alain Fischer et al. in treating young SCID-XI patients, Somia and Verma remark, "[t]o all appearances, the recipients are clinically cured, and the **fantastic promise** of gene therapy is **realized**." Somia, page 96, left column, lines 6-8 (emphasis added). While the authors temper their optimism based on the small number of patients treated and the limited duration of the study, their more recent paper does not support the Examiner's assertion that gene therapy is a "technique of the future". Paper 13, Office Action dated June 17, 2002, page 8, line 15.

Applicants note that several clinical trials, including the one conducted by the Fischer group, have been halted after a patient displayed lymphoproliferation that may be attributable to the vector, though this has not been shown definitely. *See e.g.* Stolberg SG, October 4, 2002, "Trials are halted on gene therapy", *New York Times*, page A1, column 3 (hereinafter "Stolberg"). The patient's condition may also be attributable to a family history of cancer and/or a previous chickenpox infection. However, even if it is ultimately shown that this patent's condition is due to the therapy, it would not, without more, detract from the success of the results, but would represent a side effect of the therapy. Side effects, even substantial ones, would not necessarily foreclose the use of gene therapy, particularly for diseases as devastating as SCID. *See* Stolberg, page 2, lines 35-39.

Applicants assert that the state of gene therapy art as of July 21, 2000 is more accurately represented by recent successful human gene therapy for severe combined immunodeficiency syndrome (SCID)(Cavazzana-Calvo et al., 2000, *Science* 288:669-672;

Hacein-Bey-Abina S et al., 2002, "Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy" *N Engl J Med.* 346(16):1185-1193; Rosen FS, 2002, "Successful Gene Therapy for Severe Combined Immunodeficiency" (Editorial) *N Engl J Med.* 346(16):1241-1243), angina (Losordo DW et al., 2002, *Circulation* 105(17):2012-2018; Sarkar N et al., 2001, *J Intern Med.* 250(5):373-381; Symes JF, 2000, *J Card Surg.* 15(4):283-290), and hemophilia (Kay MA et al., 2000, *Nat Genet.* 24(3):257-261). Applicants respectfully invite the Examiner's attention to the cited documents, copies of which will be provided upon request. These documents disclose the successful use of gene therapy to correct a disease phenotype and, hence, demonstrate beneficial clinical results.

The skill level in the gene therapy art is further illustrated by successful therapy in model systems for cancer therapy (Melero I et al., 2001, *Trends Immunol.* 22(3):113-115), immunotherapy (Schweighoffer T et al., 1996, *Cytokines Mol Ther.* 2(3):185-191; Toda M et al., 1999, "Herpes simplex virus as an in situ cancer vaccine for the induction of specific anti-tumor immunity" *Hum Gene Ther.* 10(3):385-393 (hereinafter Toda); Wang HY et al., 2002, "Induction of CD4(+) T cell-dependent antitumor immunity by TAT-mediated tumor antigen delivery into dendritic cells" *J Clin Invest.* 109(11):1463-1470 (hereinafter Wang)), erectile dysfunction (Schenk G et al., 2001, "Gene therapy: future therapy for erectile dysfunction", *Curr Urol Rep.* 2(6):480-487), and hemophilia (Park F et al., 2000, "Therapeutic levels of human factor VIII and IX using HIV-1-based lentiviral vectors in mouse liver" *Blood* 96(3):1173-1176). Applicants assert that these documents, among others, provide substantial guidance to the artisan of ordinary skill to practice the full scope of the claimed cells and constructs in connection with gene therapy.

Notwithstanding the foregoing argument regarding enablement of gene therapy, Applicants assert that claims 10-14 satisfy the requirements of §112, ¶1 since the specification fully enables other uses of the claimed constructs and cells, such as production of viral antigens, and screening assays for small molecules that modulate PEG-3 promoter activity. Courts have held that the enablement requirement is met if the description enables **any** mode of making and using the invention. *See e.g. Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1307 (Fed. Cir. 2001)(disclosure enabling an artisan of ordinary skill to make metal oxide coating from at least one of the suggested precursors satisfies that enablement requirement for that oxide coating); *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998)(district court did not err in granting plaintiff's motion for summary judgement, where defendant failed to show that all disclosed alternate methods of making CD34 antibodies were not enabled and where the evidence indicated that at least one method was enabled). These holdings are reflected in the Patent and Trademark Office's "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications" available, *inter alia*, at http://www.uspto.gov/web/offices/pac/dapp/oppd/1pecba.htm. In both Examples E (peptides for treating obesity) and G (gene therapy), claims are deemed allowable where no specific use is recited in the claims and the specification supports at least one use. For example, in Example G a viral vector is disclosed for use in *in vitro* protein production and *in vivo* gene therapy. Claim 1 to the viral vector is considered since the specification supports at least one use. *See e.g.* Example G ("Since claim 1 does not recite any environment of use, only one enabled use covering the scope of the claim is needed to enable the claim"). *See also* Example E ("Since no specific use is recited in these claims, one enabled use that covers the full scope of the claims is

sufficient to preclude an enablement rejection of a compound claim based on the failure to teach 'how to use'").

Applicants respectfully invite the Examiner's attention to the specification at page 26, lines 3-8, wherein Applicants have disclosed that the claimed constructs and cells may be used for the production of viral antigens, immunomodulators, hormones, cytokines, and growth factors. The use of bioreactors for the production of proteins is well known to those of ordinary skill in the art. *See e.g.* Kumar A et al., 1999, "Large-scale propagation of recombinant adherent cells that secrete a stable form of human glandular kallikrein, hK2" *Protein Expr Purif.* 15(1):62-68; Soares CR et al., 2000, "High-level synthesis of human prolactin in Chinese-Hamster ovary cells" *Biotechnol Appl Biochem.* 32(Pt 2):127-135; Stiens LR et al., 2000, "Development of serum-free bioreactor production of recombinant human thyroid stimulating hormone receptor" *Biotechnol Prog.* 16(5):703-709. Applicants assert that this disclosure is sufficient, either alone or in combination with the above-identified documents, to enable one of ordinary skill in the art to use the claimed constructs and cells in bioreactors for the *ex vivo* production of any of the named proteins.

Applicants also respectfully invite the Examiner's attention to the specification at page 2, lines 6-19, wherein Applicants have disclosed that the claimed constructs and cells may be used in screening assays for anti-cancer molecules. Molecules that inhibit PEG-3 promoter activity may be identified by the disclosed method based on a capacity to prevent or reduce the death of cells comprising the PEG-3 promoter operably linked to a gene encoding a cytotoxic gene product.

In view of the enabled uses disclosed and apparent to those of ordinary skill in the art, Applicants believe that the instant claims are fully enabled and respectfully request withdrawal of this rejection.

V. Claims Comply with 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-14 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner has alleged that claims 1 and 3 are unclear as to what sequences are being claimed since the nucleotide numbering recited in the claims appears to correspond with Figure 2, not the numbering of SEQ ID NO:1.

Applicants traverse this rejection and assert that the claim 1, as amended herein, is definite. Applicants believe that the nucleotide positions now recited by claim 1 agree with the numbering of SEQ ID NO:1. This rejection is moot with respect to claim 3 since claim 3 has been cancelled. Therefore, Applicants respectfully request withdrawal of this rejection.

VI. Claims Are Not Anticipated By the Cited Documents

A. Claims Are Not Anticipated By Hollander

The Examiner has rejected claims 2-4 and 6 under 35 U.S.C. §102(b) as allegedly anticipated by Hollander *et al.*, 1997, *J. Biol. Chem.* 272:13731-13737 (hereinafter "Hollander"). The Examiner has alleged that this document teaches a mouse *gadd34* nucleic acid of at least 15 nucleotides in length comprising a promoter sequence comprising the PEA3 site and the TATA box of SEQ ID NO:1. *See* GenCore sequence alignment, Result 3, provided by the Examiner.

Applicants traverse this rejection and assert that the pending claims are not anticipated by Hollander. These rejections are moot as to claims 2-6 since these claims have been cancelled. Claims 7-14 have been amended to be dependent on independent claim 1, which the Examiner has acknowledged is free of prior art. Therefore, Applicants respectfully request withdrawal of these rejections.

Applicants assert that new claims 38-40 are not anticipated by Hollander. For a reference to anticipate, it must teach each and every element of the claim. Hollander fails to teach an AP1 site and, therefore, does not anticipate new claims 38-40.

B. Fisher Is Not Available As Prior Art

The Examiner has rejected claims 2-14 under 35 U.S.C. §102(b) as allegedly anticipated by WO 98/42315 by Fisher et al. (hereinafter "Fisher"). *See* GenCore sequence alignment, Result 1, provided by the Examiner. The Examiner has alleged that SEQ ID NO:1 is identical to the sequence of Fisher except for three insertions, *i.e.* a C, a G and a C at SEQ ID NO:1 positions 1730, 1739, and 1894, respectively (Figure 2 positions –46, -37, and +119, respectively).

Applicants traverse this rejection and assert that Fisher is not available as prior art against claims 2-14 or new claims 38-40 under 35 U.S.C. §102(b) in view of the priority claim made herein based on U.S. Application No. 09/052,753 filed March 31, 1998, which claims priority to Fisher. Therefore, Applicants respectfully request withdrawal of this rejection.

For the foregoing reasons, Applicants believe that the claims are in condition for allowance and respectfully request prompt issuance of a Notice of Allowance.

Applicants have enclosed the fee for a three-month extension of time as required under 37 C.F.R. §1.17(a)(2). The Commissioner is hereby authorized to charge any additional fees required for this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Two copies of this page are enclosed.

Respectfully submitted,

December 17, 2002

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Enclosures
Supplemental Declaration under 37 C.F.R. §1.67(a)(1) (unexecuted)
Substitute Sequence Listing in paper and electronic form

VERSION WITH MARKINGS TO SHOW CHANGES MADE

This marked-up version was prepared with DeltaView software (v2.5.163). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

IN THE CLAIMS

Claim 1 has been **amended** as follows:

1. (AMENDED) An isolated nucleic acid comprising a PEG-3 promoter comprising the nucleotide sequence beginning with the guanosine (G) at position ~~-270~~1507 and ending with the cytosine (C) at position ~~+194~~1970 of SEQ ID NO: 1.

Claim 7 has been **amended** as follows:

7. (AMENDED) The nucleic acid of claim ~~2,~~1, wherein the ~~fragment~~nucleic acid is operably linked to a gene of interest.

Claim 11 has been **amended** as follows:

11. (AMENDED) A vector comprising the nucleic acid of any one of claims 1 and 7 to 10.

IN THE SPECIFICATION

The paragraph beginning at page 2, line 3 and ending at page 2, line 26 has been **amended** as follows:

This invention provides for an isolated nucleic acid comprising a PEG-3 promoter comprising the nucleotide sequence beginning with the guanosine (G) at position -270 and ending with the cytosine (C) at position +194 of Figure 2 (nucleotides 1507-1970 of SEQ ID NO:~~1.~~1). The invention also provides for a method for identifying an agent which modulates PEG-3 promoter activity in a cell which comprises: (a) contacting the cell with the agent wherein the cell comprises a nucleic acid comprising a PEG-3 promoter operatively linked to a reporter gene; (b) measuring the level of reporter gene expression in the cell; and (c) comparing the expression level measured in

step (b) with the reporter gene expression level measured in an identical cell in the absence of the agent, wherein a lower expression level measured in the presence of the agent is indicative of an agent that inhibits PEG-3 promoter activity and wherein a higher expression level measured in the presence of the agent is indicative of an agent that enhances PEG-3 promoter activity, thereby identifying an agent which modulates PEG-3 promoter activity in the cell. The invention provides ~~for~~ a method for treating cancer in a subject which comprises administering a nucleic acid comprising a PEG-3 promoter operatively linked to a gene-of-interest wherein the gene of interest is selectively expressed in cancerous cells in the subject and such expression ~~regulates expression of PEG-3 resulting~~results in growth suppression or death of the cancerous cells, thereby treating cancer in the subject.

The paragraph beginning at page 7, line 14 and ending at page 7, line 17 has been **amended** as follows:

This invention provides for an isolated nucleic acid comprising a PEG-3 promoter comprising the nucleotide

sequence beginning with the guanosine (G) at position -270 and ending with the cytosine (C) at position +194 of Figure 2 (nucleotides 1507-1970 of SEQ ID NO:~~1~~1).

The paragraph beginning at page 7, line 19 and ending at page 7, line 21 has been **amended** as follows:

The invention also provides an isolated nucleic acid comprising a fragment of the nucleotide sequence of ~~claim 1~~ nucleotides -270 to +194 of Figure 2 (SEQ ID NO:1) which is at least 15 nucleotides in length.

The paragraph beginning at page 7, line 25 and ending at page 7, line 28 has been **amended** as follows:

(i) a PEA3 protein binding sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position -105 and ending with the thymidine (T) at position -100 of Figure 2 (nucleotides 1672-1677 of SEQ ID NO:~~1~~1),

The paragraph beginning at page 7, line 30 and ending at page 7, line 32 has been **amended** as follows:

(ii) a TATA sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position -29 and ending with the adenosine (A) at position -24 of Figure 2 (nucleotides 1748-1753 of SEQ ID NO:~~1,~~1), or

The paragraph beginning at page 8, line 1 and ending at page 8, line 4 has been **amended** as follows:

(iii) an AP1 protein binding sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position +~~6~~5 and ending with the adenosine (A) at position +~~12~~11 of the nucleotide sequence shown in Figure 2 (nucleotides 1781-1787 of SEQ ID NO:~~1.~~1).

The paragraph beginning at page 10, line 13 and ending at page 10, line 19 has been **amended** as follows:

The invention provides for a method for treating cancer in a subject which comprises administering a nucleic acid comprising a PEG-3 promoter operatively linked to a gene-of-interest wherein the gene -of -interest is selectively expressed in cancerous cells in the subject and such espression ~~regulates expression of PEG-3 resulting~~results in growth suppression or death of the cancerous cells, thereby treating cancer in the subject.

The paragraph beginning at page 10, line 21 and ending at page 10, line 31 has been **amended** as follows:

In one embodiment of this invention, the nucleic acid consists essentially of (i) a PEA3 protein binding sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position -105 and ending with the thymidine (T) at position -100 of ~~SEQ ID NO: 1,~~Figure 2, (ii) a TATA sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position -29 and ending

with the adenosine (A) at position -24 of ~~SEQ ID NO: 1,~~Figure 2, and (iii) an AP1 protein binding sequence consisting of the nucleotide sequence beginning with the thymidine (T) at position ~~+6~~5 and ending with the adenosine (A) at position ~~+12~~11 of the nucleotide sequence shown in ~~SEQ ID NO: 1.~~Figure 2.

The paragraph beginning at page 44, line 20 and ending at page 45, line 22 has been **amended** as follows:

To define the region(s) of the FL-PEG-Prom involved in the differential expression of the PEG-3 gene during progression of the transformed phenotype in H5tsl25-transformed cells, a series of PEG-Prom deletion constructs were engineered and placed in front of the luciferase gene (Fig. 5 and 6). Deletion of the PEA3 site at position -1645 and the TATA box at position -1072 did not effect PEG promoter activity in either E11 or E11-NMT suggesting that these regions of the promoter do not contribute to basal or enhanced expression of the PEG-Prom in E11 or E11-NMT cells (Fig. 5). A further deletion at position -270 minimally inhibited promoter activity in E11-NMT cells (~19% reduction versus activity of the FL-PEG-Prom) without

significantly altering activity of the PEG-Prom in E11 cells. In contrast, removal of the PEA3 site at -104 nt with retention of the TATA box at position -24 and the AP1 site at +8 bp resulted in a reduction in basal promoter activity in both E11 and E11-NMT cells. The activity of this mutant PEG-Prom was 15- and 4-fold lower, respectively, than the activity of the FL-PEG-Prom in E11-NMT and E11 cells (Fig. 5). In effect, this promoter deletion eliminated the enhanced expression of the PEG-Prom in E11-NMT versus E11 cells, indicating that the PEA3 site at -104 is a primary determinant of the enhanced activity of PEG-3 in progressed H5ts125-transformed RE cells. Internal deletions at position -1167 to -536 and -~~1267~~1287 to -~~536~~361 resulted in similar levels of luciferase activity in E11-NMT and E11 cells as observed with the deletion mutant containing a deletion at position -270. Internal deletions engineered between -1167 to -142 and -1590 to -142 resulted in a further decrease in promoter activity in both E11 and E11-NMT cells, with the most profound effect apparent in E11-NMT cells (~41% reduction in activity in comparison with the FL--PEG-Prom). In contrast, deletion of the promoter regions from -142, -536 or -~~1287~~1167 with retention of the remainder of the PEG-Prom completely abolished PEG promoter activity (Fig. 5).

These results implicate the PEA3 transcription site (at position -104), the AP1 transcription site (at position +8) and the TATA box (at position -24) as primary determinants of basal PEG-Prom activity in E11 and E11-NMT cells.

The paragraph beginning at page 56 line 22 and ending at page 57 line 9 has been **amended** as follows:

Nuclear extracts were prepared from 2 to 5 X 10^8 cells as described by Dignam *et al.* (1983). The sequence of probes were as follows: wild-type AP1, 5'CGCAGATTGACTCAGTTCGC3' (SEQ ID NO:5)/ [5']3'GCGTCTAACTGAGTCAAGCG[3']5' (SEQ ID NO:6); mutant AP1, 5'CGCAGATAAACTACGTTCGC 3' (SEQ ID NO:7)/ [5'] 3' GCGTCTATTTGATGCAAGCG [3'] 5' (SEQ ID NO:8); wild-type PEA3, 5' GTGTTGTTTTCCTCTCTCCA 3' (SEQ ID NO:9)/ [5'] 3' CACAACAAAAGGAGAGAGGT [3'] 5' (SEQ ID NO:10); and mutant PEA3', 5' GTGTTGTTCCCATCTCTCCA 3' (SEQ ID NO:11)/ [5'] 3' CACAACAAGGGTAGAGAGGT [3'] 5' (SEQ ID NO:12). The double-stranded oligonucleotides were labeled with ^{32}P-ATP (Amersham) and T4 polynucleotide kinase. The labeled probes were then incubated with nuclear extract at RT for 30 min. The reaction mixture consisted of ^{32}P-labeled deoxynucleotides (>5000 cpm), 2 µg of poly(dI-dC) and 10 µg of nuclear protein extract with 10 mM HEPES (pH 7.5), 50 mM KCI, 5 mM MgCI2, 0.5 mM EDTA, 1 mM DTT and 12.5% glycerol.

After incubation for 30 min at RT, the reaction mixtures were electrophoresed on a 5% polyacrylamide gel with 0.5 X TBE (160V for 3 h). The gel was dried and autoradiographed. Nuclear extracts were also incubated with a 10- or 100-fold molar excess of cold competitor oligonucleotide or cJun (AP1), PEA3 or actin antibody (1 or 5 µtogether with the ^{32}P-labeled probe.

The abstract of the disclosure at page 69 has been **amended** as follows:

Abstract of the Disclosure

This invention provides ~~for~~ an isolated nucleic acid comprising a PEG-3 promoter comprising the nucleotide sequence ~~beginning with the guanosine (G) at position~~of -270 ~~and ending with cytosine (C) at position~~to +194 of ~~SEQ ID NO: 1.~~Figure 2. The invention also provides ~~for~~ a method for identifying an agent ~~which~~that modulates PEG-3 promoter activity ~~in~~using a cell which comprises~~: (a) contacting the cell with the agent wherein the cell comprises a nucleic acid comprising~~ a PEG-3 promoter operatively linked to a reporter gene~~; (b) measuring the level of reporter gene expression in the cell; and (c) comparing the expression level measured in step (b) with~~

~~the reporter gene expression level measured in an identical cell in the absence of the agent~~, wherein ~~a lower~~reduced reporter gene expression ~~level measured~~ in the presence of the agent is indicative of an agent that inhibits PEG-3 promoter activity and wherein ~~a higher~~increased reporter gene expression ~~level measured~~ in the presence of the agent is indicative of an agent that enhances PEG-3 promoter activity~~, thereby identifying an agent which modulates PEG-3 promoter activity in the cell~~. The invention provides ~~for~~ a method for treating cancer in a subject which comprises administering a nucleic acid comprising a PEG-3 promoter operatively linked to a gene-of-interest, wherein the gene -of -interest is selectively expressed in cancerous cells in the subject and such expression ~~regulates expression of PEG-3 resulting~~results in growth suppression or death of the cancerous cells~~, thereby treating cancer in the subject~~.